**Experiment Number:** S0916
**Route:** IV, Gavage
**Species/Strain:** Rats/F344

**Toxicokinetics Data Summary**
**Compound:** Tamoxifen citrate / **Analyte:** Tamoxifen
**CAS Number:** 54965-24-1

**Request Date:** 7/11/2023
**Request Time:** 10:03:16
**Lab:** RTI

**Female**

**Treatment Group (ug/mL) Single Dose**

| | **300 IV Plasma[a,c]** | **300 IV Plasma[b]** | **300 IV Plasma[a,d]** |
|---|---|---|---|
| Cmax_obs (ug/L) | 16.4 | | 10.6 |
| Tmax_obs (hour) | 0 | | 0.5 |
| Beta ($hour^{-1}$) | 0.395 | | 0.565 |
| Beta Half-life (hour) | 1.76 | | 1.23 |
| AUC_0-T (hr*ug/L) | 17.5 | | 14.7 |
| AUCinf_pred (hr*ug/L) | 42.8 | | 35.6 |

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| | Treatment Group (ug/mL) Repeated Dose | | |
|---|---|---|---|
| | **300 Gavage Plasma[a]** | **300 Gavage Plasma[a]** | **300 Gavage Plasma[a,e]** |
| Cmax_obs (ug/L) | 11.9 | 15.4 | 21.9 |
| Tmax_obs (hour) | 0.25 | 0.25 | 0.25 |
| Beta ($hour^{-1}$) | 0.372 | 0.301 | 0.080 |
| Beta Half-life (hour) | 1.87 | 2.30 | 8.70 |
| AUC_0-T (hr*ug/L) | 14.9 | 32.6 | 55.1 |
| AUCinf_pred (hr*ug/L) | 104 | 82.2 | 77.2 |

LEGEND

MODELING SOFTWARE
WinNonlin, Version 1.0

MODELING METHOD & BEST FIT MODEL

[a]WinNonlin, Version 1.0; SCI Software, Lexington, KY, noncompartmental model for bolus iv dosing (Model 201), A uniform weighting scheme was used. Includes Study I (I1,I3), Study N (N1,N3,N4).

[b]WinNonlin, Version 1.0; SCI Software, Lexington, KY, For animal I2, all TAM concentrations were below LOQ. Hence, no pharmacokinetic parameters were determined. Includes Study I (I2). Study J (J1,J2,J3) 100ug gavage, K (K1,K2,K3) 300 ug gavage, L (L1,L3,L4) 100 ug gavage were not modeled because plasma samples contained TAM at concentrations greater or equal to LOD at not more than five time points for a given animal. Study M female rats (M1, M3, and M4) 300 ug gavage treated for 29 days data were not modeled because plasma samples were out of range.

EXCEPTIONS

[c]Co back extrapolated,2 hours equals the time of last sample where TAM concentration is greater or equal to LOQ

[d]C0 was set equal to the first observed concentration. 2 hours equals the time of last sample where TAM concentration is greater or equal to LOQ

[e]t equals 8 hour was excluded from the estimation of Beta because TAM was less than the LOQ.

ANALYTE
Tamoxifen

TK PARAMETERS

Cmax_obs = Observed or Predicted Maximum plasma (or tissue) concentration
Tmax_obs = Time at which Cmax predicted or observed occurs
Beta = Hybrid rate constant of the beta phase
Beta Half-Life = Half-life for the beta phase
AUC_0-T = Area under the plasma concentration versus time curve, AUC, from time ti (initial) to tf (final), AUClast
AUCinf = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

TK PARAMETERS PROTOCOL

ANALYSIS METHOD

On the day prior to dosing, jugular cannula were surgically implanted. Animals received a single bolus intravenous into the lateral tail vein (Study I) or a single dose by oral gavage (Studies J and K). Blood samples were collected from each animal via the indwelling cannula at 14 post-dosing timepoints then by cardiac puncture (under terminal anesthesia for the 15th timepoint).

TK_INTRAVENOUS PLASMA

<u>300 ug/mL Study I (I1,I2,I3)</u>

Because TAM was present at concentrations less than the LOQ for the majority of the samples, TAM concentration-time data were analyzed for Studies I and N only. DMT concentration-time profiles were not analyzed as none of the plasma samples were greater or equal to the LOQ. Trans-4-hydroxytamoxifen was seen in only one of the 318 plasma samples. For the single dose study (Study I) no sample was collected prior to dosing (T0) and the concentration at T0 (C0) was back-extrapolated.

TK PARAMETERS PROTOCOL

TK_GAVAGE PLASMA

100 ug/mL Study J (J1,J2,J3), 300 ug/mL Study K (K1,K2,K3)

Because TAM was present at concentrations less than the LOQ for the majority of the samples, TAM concentration-time data were analyzed for Studies I and N only. DMT concentration-time profiles were not analyzed as none of the plasma samples were greater or equal to the LOQ. Trans-4-hydroxytamoxifen was seen in only one of the 318 plasma samples. For the single dose study (Study I) no sample was collected prior to dosing (T0) and the concentration at T0 (C0) was back-extrapolated.

ANALYSIS METHOD

Animals were dosed once daily for 28 consecutive days by oral gavage. After Day 28 dosing, jugular cannula were surgically implanted in the repeated dose animals. On Day 29, immediately prior to dosing, a blood sample was obtained (To samples). Then, a final oral dose was administered (Study L and M) or intravenously (Study N). Blood samples were collected from each animal via the indwelling cannula at up to 20 post-dosing timepoints then by cardiac puncture (under terminal anesthesia for the 21st timepoint) .

TK_GAVAGE PLASMA

100 ug/mL Study L (L1,L3,L4), 300 ug/mL Study M (M1,M3,M4), 300 ug/mL Study N (N1,N3,N4)

Study N (repeated administration study) were analyzed as if they were obtained after a single dose of TAM. Because TAM was present at concentrations less than the LOQ for the majority of the samples, TAM concentration-time data were analyzed for Studies I and N only. DMT concentration-time profiles were not analyzed as none of the plasma samples were greater or equal to the LOQ. Trans-4-hydroxytamoxifen was seen in only one of the 318 plasma samples.